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CADHERINS

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CONTENTS

CELL ADHESION: General Considerations

The evolution of specific mechanisms for cell adhesion was one of the crucial steps in the development of metazoan organisms. During embryonic development adhesive interactions play a major role in triggering a variety of morphogenetic processes throughout the organism, some of which have immediate consequences while others have long-term effects that lead to the assembly of single cells into organs. Such interactions may involve either direct cell-cell contact or adhesion to extracellular matrix (ECM) networks. These processes involve two critical and distinct stages, namely a binding event mediated through cell-surface receptors, which specifically and directly interact with the external ligand, and a morphogenetic event, which depends on the activity of force-generating cytoskeletal systems within the cells. Obviously the two processes must be well coordinated in time and space in order to yield various tissue forms and, eventually, an embryo. Long-range events induced by the various adhesive interactions include a wide variety of

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cellular activities such as cell locomotion, proliferation, and differentiation. Beyond the local adhesive interaction, each of these processes involves the generation and propagation of specific signals that affect the gross behavior of the cells through post-translational modifications, formation and translocation of second messengers, and the modulation of specific gene expression.

It appears that the three processes mentioned above-- receptor-mediated binding, cytoskeleton-driven morphogenesis, and the effects on cell behavior-- are highly interdependent. As is discussed below, for example, the assembly of cytoskeletal structures in cells is driven by local adhesions, but in turn this assembly affects the adhesive process. Moreover, changes in the state of cell differentiation often have an effect on the expression of adhesion molecules or on the organization of the cytoskeleton. Therefore, elucidation of the mechanisms involved in cell adhesion, at the molecular level, requires a multidisciplinary approach, conducted in parallel at all these levels. This challenge is particularly demanding in view of the large number and complexity of cells that participate in embryonic morphogenesis and the inherent plasticity of these processes.

A conceptual breakthrough regarding morphogenesis occurred over 30 years ago, following the works of Holtfretter (Townes & Holtfretter 1955), Moscona (1961), Trinkaus (1963), and others, who demonstrated the critical role of adhesion in morphogenesis and the fact that suspended embryonic cells retain their capacity to reaggregate and sort-out in a histotypically-specific manner (reviewed in Albelda 1991; Edelman et al 1990; Edelman & Thiery 1985).

The next major step included the identification of specific adhesion molecules that apparently mediate these processes and most likely trigger the cytoplasmic events that drive morphogenesis. The systematic search for adhesion molecules started about twenty years ago and is still one of the most active and central research fields in cell and developmental biology.

Since then, a multitude of adhesion molecules have been described that are classified into several distinct and structurally diversified families, including integrins, adhesion molecules of the Ig superfamily, LEC-CAMs, cadherins, and more (Albelda 1991; Albelda & Buck 1990).

Integrins are heterodimeric transmembrane receptors that mediate cell-matrix and sometimes cell-cell adhesion (Albelda & Buck 1990; Hynes 1987). They consist of three major and a few minor β chains that may associate with more than ten different α chains. Adhesion molecules of the Ig superfamily mediate Ca^{2+}-independent cell-cell adhesion of either a homophilic or heterophilic nature (Williams & Barclay 1988). Molecules belonging to this group, notably N-CAM, were among the first adhesion molecules isolated and characterized (Edelman & Thiery 1985). The homing receptors of the LEC-CAM family are found mainly on leukocytes, platelets, and endothelial

cells, and play a major role in the targeting and activation of immune cells throughout the body (Albelda & Buck 1990; Butcher 1990).

The subject of this review is the cadherin family, which is involved in Ca^{2+}-dependent intercellular interactions. These molecules are especially relevant for morphogenetic processes since they provide the transmembrane association of the cytoskeleton with the plasma membrane at the site of cell adhesion. We discuss the structural basis for cadherin activity and the mechanisms by which it may affect cell shape, dynamics, and cell fate.

CADHERIN-MEDIATED MORPHOGENESIS

It is widely appreciated that embryonic morphogenesis depends, at the cellular and molecular levels, on a large number of interdependent processes that concertedly affect tissue form and function. These include cell proliferation, differentiation, motility and adhesion. It is far beyond the scope of this article to discuss the contribution of each of these factors and the spatial and temporal mechanisms that control them. Nevertheless, it is apparent that adhesive interactions play a key role in all these events, and thus adhesion molecules may rightfully be regarded as "morphoregulatory" molecules (Edelman et al 1990).

The requirement for an efficient coupling of adhesion and contractility during morphogenesis has been amply discussed, based on theoretical and experimental grounds (Edelman & Thiery 1985; Ettensohn 1985; Odell et al 1981). One such adhesion-dependent mechanism may be defined as a selective segregation process, whereby the expression of a specific adhesion molecule in a particular subpopulation of cells leads to a selective homotypic sorting. It is likely that such processes were responsible for the sorting described by Townes & Holtfretter (1955), which has become almost a compulsory reference in developmental biology text books. They showed that cells tend to cluster homotypically, according to their histogenetic origins, and then form characteristic tissue patterns. Obviously, no molecular information was available at that time.

Recent experiments have directly addressed the question as to whether specific differences in one particular group of adhesion molecule, namely cadherins, could account for similar histogenetic segregation. The experimental strategy was to mix prelabeled cells transfected with cDNAs encoding different cadherins, and then examine the cell organization throughout the clusters. For example, L-cells expressing E- and P-cadherins, mixed in vitro or introduced into reconstituted embryonic lung tissue (Nose et al 1988), displayed highly selective segregation. However, it is known that the requirement for an exclusive homophilic interaction is not absolute. It was shown that when A-CAM (N-cadherin) and L-CAM (E-cadherin) expressing cells

are mixed, there is a preference for the formation of homotypic contacts, yet heterotypic (and apparently heterophilic) junctions are also found (Volk et al 1987). These results certainly confirm that a homophilic preference (i.e. higher affinity) exists, yet indicate that there is also a weaker, but significant and specific, reactivity between cadherins of different types. One should also appreciate the fact that the selectivity of cadherin-mediated interactions may be affected by the relative amount of cadherin expressed. Thus, transfected clones expressing different levels of the same cadherin may sort away from each other (Friedlander et al 1989).

Another morphogenetic process in which cadherins appear to play an important role is cell condensation, the transition of cell populations from a dispersed pattern into a compact one. One example for such condensation is the compaction of blastomers or equivalent processes during early embryonic development. In fact, one of the first functions assigned to a cadherin (uvomorulin) was the induction of cell compaction in the mouse morula (Hyafil et al 1980, 1981). However, it was noted that some uvomorulin was already present on the surface of the unfertilized egg and its further synthesis initiated at the two-cell stage, long before compaction actually occurred (Vestweber et al 1987). This suggests that the mere presence of the E-cadherin protein is insufficient for inducing cell condensation and that additional events (post-translational modification or attachment to the cytoskeleton) are needed. A role for cadherins in blastomer condensation during early stages of development was also suggested by perturbation experiments carried out with *Xenopus* embryos using an anti-sense approach. In *Xenopus*, the major (possibly the only) cadherin present in pre-mid blastula transition (MBT) embryos is EP-cadherin (Ginsberg et al 1991; Table 1). In a series of experiments it was shown that injection of anti-sense oligonucleotides into the oocytes dramatically suppressed the levels of EP-cadherin mRNA and protein in the embryos. Examination of such embryos by light and electron microscopy revealed a marked effect on intercellular adhesion, especially between the inner blastomers. The adhesion between the outer blastomers was largely retained, which suggests that either residual EP-cadherin or another adhesion system is operative (D. Ginsberg et al, unpublished results).

A related morphogenetic process, in which cell interactions are modulated by alterations in cadherin expression, is mesenchyme to epithelium transition or vice versa (Ekblom 1989). Demonstration of such relationships was obtained from studies on cadherin expression in intact embryos and from transfection of cadherin cDNA into cultured mesenchymal cells. Examples of the mesenchyme-epithelium transition are well described in the literature, mostly showing the correlation between epithelialization events and expression of specific cadherins. For example, somite development involves epithelialization of a mesenchymal rod, the segmental plate. This process is

Table 1 List of vertebrate cadherins[a]

Cadherin type	Tissue	References[d]
N-cadherin[b]		
chicken	Lens	Lagunowich & Grunwald 1989; Maisel & Atreya 1990
	Early embryo	Duband & Thiery 1990; Hatta et al 1987
	Nerves	Bixby & Zhang 1990; Dalseg et al 1990; Hatta et al 1988; Matsunaga et al 1988a,b
	Muscle	Knudsen 1990; Wheelock 1990
	Ear	Raphael et al 1988
human	Nerves	Reid & Hemperly 1990; Walsh et al 1990
	Endothelium	Salomon et al 1992
mouse	Nerves	Miyatani et al 1989
rat	Muscle	Pouliot et al 1990
bovine	Endothelium	Liaw et al 1990
Xenopus	Early embryo	Choi & Gumbiner 1989; Choi et al 1990; Detrick et al 1990; Ginsberg et al 1991; Fujimori et al 1990
zebrafish	Early embryo	
	Muscle	S. Bitzur & B. Geiger, in preparation
R-cadherin		
chicken	Retina	Inuzuka et al 1991
E-cadherin[c]		
mouse	Early embryo	Nagafuchi et al 1987; Peyrieras et al 1983; Vestweber et al 1987
	Skin	Hirai et al 1989
	Ovaries	Hashimoto et al 1989
chicken	Early embryo	Gallin et al 1987; Shames et al 1991
dog	Kidney	Behrens et al 1989; Gumbiner & Simons 1987
human	Epithelium	Frixen et al 1991; Mansouri et al 1988; Shimoyama et al 1989a; Shino et al 1991
	Placenta	Fisher et al 1989
bovine	Epithelium	Jones 1988
Xenopus	Early embryo	Choi & Gumbiner 1989; Herzberg et al 1990
P-cadherin		
mouse	Placenta	Nose et al 1987
	Skin	Hirai et al 1989
human	Epithelium	Shimoyama et al 1989b
bovine	Endothelium	Liaw et al 1990
EP-cadherin		
Xenopus	Early embryo	Ginsberg et al 1991
B-cadherin		
chicken	Early embryo	Napolitano et al 1991
T-cadherin		
chicken	Early embryo	Ranscht & Bronner 1991
M-cadherin		
mouse	Muscle	Donalies et al 1991
Desmogleins		Goodwin et al 1990; Koch et al 1990; Wheeler et al 1991
Desmocollins		Holton et al 1990; Jones et al 1988

[a] Only representative molecules with known sequences are included. Evidence for the existence of additional cadherins (i.e. eight new cadherins reported by Suzuki et al 1991) is discussed in the text. [b] Also known as A-CAM or N-Cal CAM. [c] Also known as uvomorulin, L-CAM, arc-1, cell CAM 120/80. [d] Partial list.

accompanied by an apparent increase in N-cadherin levels (Duband et al 1987, 1988; Hatta et al 1987). At a later stage, the sclerotomal region of the somite loses N-cadherin expression and consequently disintegrates. Neural crest cells, another system in which N-cadherin modulation apparently affects cell organization and dynamics, lose N-cadherin expression just before their departure from the neural tube (Duband et al 1988; Duband 1990) and re-express it upon re-aggregation.

A more systematic means of studying the role of cadherins in mesenchymal-epithelial transition is the forced expression of different cadherins in fibroblastic cells, which contain little or no cadherin, or the ectopic expression of such protein in embryos. As shown by several researchers (Hatta et al 1988; Mege et al 1988; Nagafuchi & Takeichi 1988), the expression of different cadherins in culture induced an apparent epithelialization of the transfected cells. A similar approach was also used in developing *Xenopus* embryos, which misexpressed N-cadherin (Detrick et al 1990). These analyses proved rather reliable and thus became standard procedures for functional analysis of cadherins. The involvement of cadherins in epithelialization was further corroborated by antibody inhibition experiments. It was demonstrated that antibody-mediated inhibition of cadherin action resulted in the loss of epithelial shape and in stimulation of cell motility and invasiveness (Behrens et al 1989; Frixen et al 1991; Thiery et al 1988).

Another type of cadherin-mediated morphogenetic process is the folding of epithelial sheets, which occurs, for example, during the formation of the neural tube or the lens (Duband et al 1987, 1988). Such events take place following differential expression of cadherins in these tissues, namely following the switch from E-cadherin to N-cadherin expression in the neural groove or lens placode. It was further proposed that the gross topological movements that follow are driven by forces generated by the controlled contraction of the junctional microfilaments belt.

Obviously the folding of epithelia involves more than apical contraction alone and the local expression of a single adhesion molecule (see Odell et al 1981). Indeed, in many tissues, more than one cadherin can be found. This is the situation, for example, in the developing skin (Hirai et al 1989), endothelia (Liaw et al 1990; Salomon et al 1992), and kidney (Okada 1988). In such systems different cadherins may be present either in subpopulations of cells or even co-expressed in the same cell. The former situation, in which periodically-spaced cell collectives express distinct sets of adhesion molecules, and the border between them is responsible for the overall organization of the tissue, apparently leads to the striking patterns obtained during the development of feathers in the chick skin. These interphases between periodic L-CAM and N-CAM-containing regions appear to play a crucial role in the various levels of feather morphogenesis (Chuong & Edelman 1985).

While most of the mechanisms outlined above primarily affect morphogenesis through establishment of intercellular adhesions, cadherin-mediated interactions also appear to be involved in cytomorphogenesis, namely intrinsic changes in the shape of the individual cell. Some of these may be directly related to the transcellular forces generated in the junction area, as described above, while others may intrinsically modulate cell structure by inducing cell polarization or differentiation (Schoenenberger et al 1991; Watson et al 1990). The latter interaction is particularly interesting and challenging since it apparently involves long-range effects on cell behavior (see below).

Another morphogenetic mechanism, detected in cells plated on a cadherin-transfected "feeder layer," is cadherin-mediated guidance, which apparently promotes the migration and extension of optic axons (Bixby & Zhang 1990; Matsunaga et al 1988a,b).

These are only a few examples of morphogenetic mechanisms driven by cellular interactions in which cadherins appear to play an important role. We now describe the cellular domain in which cadherins reside, namely adherens-type junctions.

CADHERINS AND ADHERENS-TYPE JUNCTIONS

To better appreciate the mechanism responsible for cadherin-mediated force generation, we briefly discuss the biogenesis of adherens-type junctions (AJ). Immunolocalization studies with intact tissues and cultured cells pointed to the specific association of cadherins with AJ (Boller et al 1985; Geiger 1989; Hirano et al 1987; Volk & Geiger 1986a,b). This particular class of cell contacts is characterized by its association with actin filaments, vinculin, and several actin-associated proteins. As was previously described, AJ may be formed either with other cells or with the extracellular matrix. Members of the intercellular group of cell adhesions, which we are discussing here, are widely distributed in cells and tissues and display a variety of configurations. In polar epithelial cells, AJ are part of a junctional complex (Farquhar & Palade 1963) flanked by the more apical tight junction and the more basal desmosomes. Each of these junctional elements contains a unique set of components and has distinct functional assignments (Geiger 1989; Geiger et al 1990a; Gumbiner 1988).

Analysis of AJ organization suggests that they might be subdivided into three major structural domains. These include a cytoskeletal domain consisting of actin filaments and several associated proteins (e.g. α-actinin), a plaque structure, which links these filaments to the membrane, and integral membrane components, which are directly involved in the adhesive interaction. It was also noted that while the cytoskeletal domains of all AJ (intercellular and cell-matrix) are molecularly similar, both the plaque and membrane domains

are diversified (Geiger et al 1990a). Thus besides common compounds such as vinculin, zyxin, etc (Geiger & Ginsberg 1991), there are proteins that associate selectively with matrix- (i.e. talin) or intercellular- (i.e. plakoglobin, catenins) adhesions. The integral membrane domains of the respective junctions were shown to contain distinct classes of molecules, integrins, and cadherins, the fine specificity of which may vary from one cell type to the other. Localization of cadherins in AJ was based on both electron microscopic (Boller et al 1985; Volk & Geiger 1986b) and immunofluorescence labeling (Volk & Geiger 1986a; Volk et al 1984). It was noted, however, that cadherins are not always strictly restricted to these junctional sites. Thus for example in cultured MDCK cells, E-cadherin was detected also in non-junctional regions of the basolateral membrane (Gumbiner & Simons 1987; Gumbiner et al 1988), and in cultured human endothelial cells, N-cadherin appears to be largely extrajunctional (Salomon et al 1992).

The associations of cadherins with AJ fits well with the known Ca^{2+}-dependence of both the adhesion molecules and of AJ. It was shown that upon transfer of cells to low Ca^{2+} medium, AJ (as well as desmosomes) readily split, thus exposing the specific cadherin on the retracting surfaces (Volk et al 1990). This was followed by vigorous contraction of the two cells away from each other, presumably driven by the junctional microfilament belt. At later stages, the filaments apparently detached from the cell surface along with vinculin (Volberg et al 1986) and at least part of the associated cadherin (Kartenbeck et al 1991).

Interestingly, cadherin-mediated interactions appear to affect not only the integrity of AJ, of which they are integral components, but also the neighboring tight junction (Gumbiner & Simons 1987; Gumbiner et al 1988), gap junctions (Mege et al 1988), and the fodrin-based membrane-skeleton (McNeill et al 1990).

CADHERIN STRUCTURE

Most of the structural information currently available on cadherins is derived from analysis of primary sequences obtained following cloning of the respective cDNA. Earlier works have established that cadherins are surface glycoproteins ranging in apparent molecular mass between 120–140 kd. The extensive sequence data that have accumulated over the last several years provide some insights into the fine structure of the different cadherins and to the structural relationships between them. These studies disclose a remarkable degree of homology that justifies the definition of a cadherin superfamily. Most members of this family display roughly similar division into sub-domains, including presequences that are cleaved upon processing, a large extracellular domain, a single hydrophobic transmembrane region, and a cytoplasmic tail.

To illustrate the major structural elements in cadherins, we have aligned the sequences of 16 different cadherins (see list in Figure 1 legend) and determined the percent identity for each position. For comparison we have examined the similarity between members of the N-cadherin subfamily in different species (Figure 1, *bottom*), which show a higher degree of inter-homology. Analysis of the sequences revealed three major interhomologous ectodomains (EC 1–3), each about 110 amino acid long (Takeichi 1990). In addition, one or two less homologous repeats (EC4 and 5) can be identified more proximally to the membrane.

Some regions of all cadherins show a particularly high degree of conservation. Hallmarks of these molecules are the LDRE sequences found in EC1, EC2, and EC4, and the DXNDNXP sequence present in all four N-terminal ectodomains. In addition, there are four cysteine residues located in EC5, close to the transmembrane region, which are present in the same location in all cadherins. Moreover, conserved regions in the cytoplasmic domain are noted. Additional sites throughout the molecule that have specific functional assignments are discussed below.

A related overall structure is found in the desmogleins and desmocollins, the transmembrane proteins of the desmosomes (Goodwin et al 1990; Holton et al 1990; Jones 1988; Koch et al 1990; Wheeler et al 1991). Sequence homology with the cadherin ectodomains including the presence of the DXNDN site and several additional typical sequences was disclosed. The cytoplasmic tail, on the other hand, which is highly conserved between cadherins, bears no similarity to the respective domain in desmogleins or desmocollins. It is conceivable that these differences reflect the capacity of the latter to interact with a different cytoskeletal network, the intermediate filaments system.

Other members of the cadherin superfamily, which deviate from the structural scheme presented here, are the truncated (T) cadherins found in the nervous system. These molecules lack most of the cytoplasmic domain and appear to be prominent components of many neuronal cells (Ranscht et al 1991). It is thought that T-cadherin is anchored in the plasma membrane by means of a glycosyl phosphatidylinositol glycan instead of a transmembrane domain, yet it can induce Ca^{2+}-dependent cell aggregation in transfected cells. The mechanism of action of these molecules is not yet clear.

Another issue to be considered is the diversity of cadherins, namely what is the total number of cadherins present within the same organism, and what are the structural and functional differences between them. An unequivocal answer to this question is not available yet and thus presents a significant challenge for future research. The difficulties stem from the fact that the currently available information is derived from incomplete sequence data obtained for cadherins of different species. It is nevertheless apparent that the

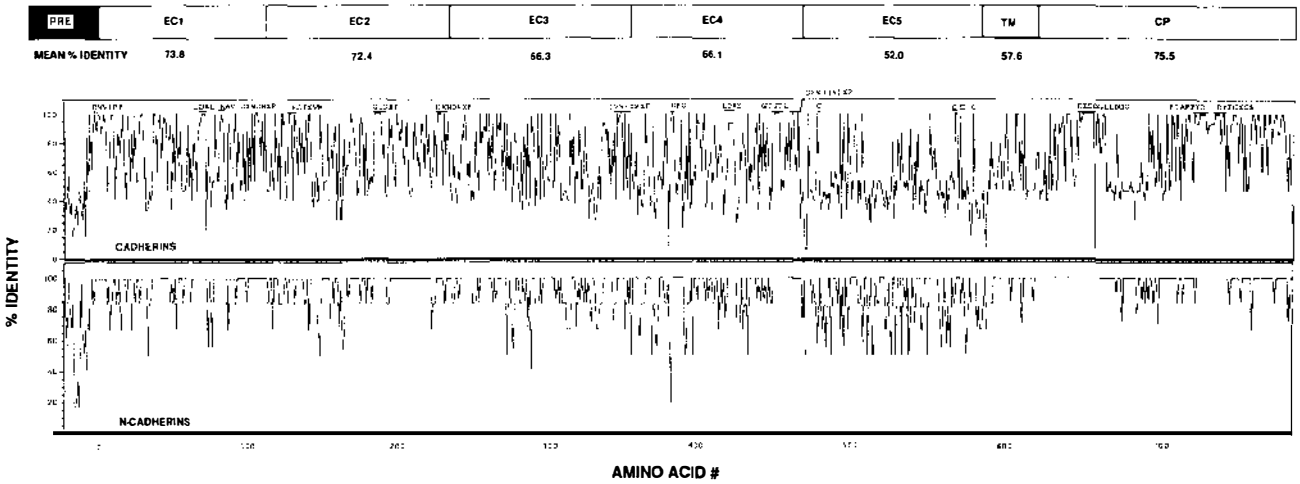

Figure 1 Amino acid homology between different cadherins. The top panel schematically depicts the cadherin molecule divided into various domains including the presequences (PRE), the five ectodomains (EC1–5), the transmembrane region, and the cytoplasmic (CP) domain. For sequence comparisons, 16 different cadherins were aligned using the "Pileup" multisequence alignment program (Devereux et al 1984) and the percent identity of the most frequent amino acid at each position was calculated. In the middle panel, comparison between all the cadherins tested is shown, and in the lower, only the N-cadherins are compared. In addition, the mean percent identity for each domain of the mature molecule was computed. The comparisons reveal some of the conserved regions of the molecules which are marked in the middle panel and discussed in the text. The sequences selected for comparison are the following: human, bovine, mouse, chicken, *Xenopus*, and zebrafish N-cadherins (Walsh et al 1990; Liaw et al 1990; Miyatani et al 1989; Hatta et al 1987; Choi & Gumbiner, 1989; S. Bitzur & B. Geiger, in preparation); chicken R-cadherin (Inuzuka et al 1991); human, bovine and mouse P-cadherins (Shimoyama et al 1989b; Liaw et al 1990; Nose et al 1987); human, mouse, and chicken E-cadherins (Mansouri et al 1988; Nagafuchi et al 1987; Gallin et al 1987); *Xenopus* EP-cadherin (Ginsberg et al 1991); chicken B-cadherin (Napolitano et al 1991); and mouse M-cadherin (Donalies et al 1991).

number of different molecules is quite large, well beyond the three major subfamilies, i.e. N-, E- and P-cadherins. This becomes apparent mainly by extensive cloning efforts of cadherins in the same species. Indeed, such attempts including PCR-mediated cloning have revealed a large number of molecules, as listed in Table 1 (see also, Suzuki et al 1991). How different should cadherins be to display distinct binding specificity? The answer to that question is not yet clear, although it had been shown that the homophilic restriction may be affected by only minor alterations in sequences like those flanking the HAV site. Moreover, functional variations may affect not only the homophilic specificity, but also molecular properties, which depend on other functional sites such as those described below.

FUNCTIONAL SITES OF CADHERIN MOLECULES

Some of the conserved sites along cadherins are shown to contribute, in different ways, to the activity of the molecule, namely to Ca^{2+}-dependent cell-cell adhesion. As is shown below, most of this information is based on transfection experiments with mutated cDNA, combined with a functional cell adhesion assay. Some of the sites involved in the various molecular interactions of cadherins are discussed below.

Attempts to identify the homophilic-binding site through which cadherins interact with each other suggest that the N-terminus is important for the adhesive activity. As shown in Figure 1 and in Shirayoshi (1986a), the N-termini of mature cadherin molecules are highly conserved, which suggests that this region plays an indispensable role in adhesion. The similarity in this region starts 5–7 amino acids N-terminal to the cleavage site, which suggests that proper processing of the precursor molecule might be important for cadherin function. This notion gained further support from studies in which mutant E-cadherin cDNA with an altered protease-sensitive site was transfected into cells and their adhesive capacity determined (Ozawa & Kemler 1990). It was found that the uncleaved molecules could not support adhesive interaction, while cleavage of the precursor region by an exogenous protease resulted in the activation of the molecule.

The specificity-determining region in cadherins also appears to reside in the N-terminal part of the molecule. This observation is based on experiments in which segments of different sizes are switched between cadherins, which indicates that the site(s) determining the specificity of interaction depend on the 113 N-terminal amino acids (Nose et al 1990; Takeichi 1990). The precise location of the cadherin-binding site and specifier and the dependence of binding on other defined regions along the molecule are not clear. To obtain a definitive answer, one should address several questions: Does the interaction between cadherins occur via a single site, i.e is the binding site interacting

with the same structure on the partner molecule (homo-epitopic), or are there two or more distinct regions directly involved in the linkage (hetero-epitopic, see Figure 2)? This question is not an easy one to approach experimentally since effects on binding activity may be indirect and involve regions that modulate the overall protein structure, accessibility of the actual binding sites, or the capacity to anchor to the cytoskeleton. For example, C-terminal deletions suppress the function of the molecules although they clearly do not directly affect the external binding site (Nagafuchi & Takeichi 1988). Moreover, modifications in the EC5 domain affect the reactivity and stability of the molecule although they are not included in the 113 amino acid segment described above (Ozawa et al 1990b).

Another aspect of the same question is whether the homophilicity-determining site on cadherins is an integral part of the binding epitope or whether it is located in a distinct region of the molecule. While this question is still largely open, there are indications that specific sequences might be involved in the cadherin-mediated recognition. One such epitope is the HAV sequence located in EC1 in essentially all cadherins (Figure 3). The involvement of the HAV sequence in cadherin action is supported by the capacity of a HAV-containing synthetic peptide to effectively block cadherin-mediated morphogenesis (Blaschuk et al 1990b). Furthermore, the amino acids immediately flanking the HAV sequence were shown to play an important role in determining cadherin specificity (Takeichi 1990). It is interesting to note that sequences along the EC1, including the HAV-region, bear a

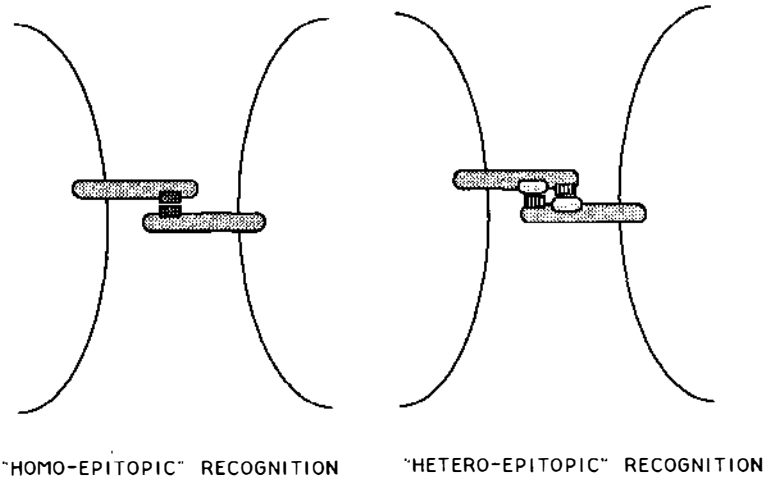

Figure 2 A comparison between putative "homo-epitopic" and "hetero-epitopic" mechanisms of homophilic binding. In the former, a single site is involved directly in the self-recognition, while in the latter two or more regions partake.

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hNcad   QIARFHLRAHAVDINGNQVE
bNcad   LIARFHLRAHAVDINGNQVE
mNcad   LIARFHLRAHAVDINGNQVE
cNcad   QIASFHLRAHAVDVNGNQVE
xNcad   QIATFHLRAHAVDVNGNQVE
zNcad   HIPNFHLRAHAVDINGNQME
cRcad   ERASYHLRAHAVDMNGNKVE
hPcad   EIAKYELFGHAVSENGASVE
mPcad   KIVKYELYGHAVSENGASVE
hEcad   RIATYTLFSHAVSSNGNAVE
mEcad   AIAKYILYSHAVSSNGEAVE
cBcad   HINKYHLYSHAVSENGKPVE
cEcad   KIDRYTLLSHAVSASGQPVE
xEPcad  EYDKYVLSSHAVSENGSPVE
mMcad   KTDRFRLRAFALDLGGSTLE
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Figure 3 Comparison of amino acids sequences corresponding to the HAV region of different cadherins (see list in legend to Figure 1). The homology is apparent as well as the diversity in the sequences flanking the HAV segment.

remarkable homology to influenza strain A hemagglutinin (Blaschuk et al 1990a).

Another physiologically-important question concerns the Ca^{2+}-binding region in cadherins. The effect of Ca^{2+} ions on cadherins was apparent from the Ca^{2+} requirement for the adhesive function (Takeichi 1990), and the apparent effect of Ca^{2+} on the protein structure and protease sensitivity (Hyafil et al 1980, 1981; Takeichi 1990). Analysis of deduced amino-acid sequences of E-cadherin did not disclose any of the known consensus sequences for Ca^{2+}-binding (EF-hands, for example) (Ringwald et al 1987), yet putative Ca^{2+}-binding sites were identified along the extracellular region. These consist of the sequence DXNDNXP, which appears, with minor variations, in each of the four ectodomains and complementary aspartic acid-rich stretches ("b" sites, Ozawa et al 1990a). Furthermore, a decapeptide KVSATDADDD corresponding to the end of the EC1 in E-cadherin had the capacity to complex Ca^{2+} ions, and a single amino acid substitution (aspartic acid in position 134 to alanine or lysine) abolished the adhesive potential of the molecule (Ozawa et al 1990a).

Another physiologically important domain is the cytoplasmic domain, which contains the catenin-binding site(s) and is highly preserved throughout evolution and between different cadherins. Both sequence analyses (Figure 1) and immunological data (Geiger et al 1990b) suggest that most of the cytoplasmic domain displays a high degree of homology and that its presence is essential for cadherin function (Nagafuchi & Takeichi 1988). Systematic functional analysis of deleted molecules confirmed that the 72 C-terminal amino acids are essential for catenin binding (Ozawa et al 1990, and see below).

In addition to those sites whose putative functions are directly demonstrated,

there are other highly conserved regions, the LDRE sequence for example, whose functions remain to be elucidated. The glycosylation sites are another structural entity whose function is not clear. The presence of N-linked carbohydrates on cadherins was first noted by direct biochemical analyses (Damsky et al 1983; Peyrieras et al 1983, 1985) and later supported by computer analysis of protein sequences (Hatta et al 1988). However, the role of the linked oligosaccharides is still unclear. Tunicamycin, which effectively blocks N-glycosylation, had no apparent effect on E-cadherin activity (Gallin et al 1987; Shirayoshi 1986b). It remains to be determined whether this modification has an effect on the binding specificity of cadherins or on their stability.

The molecular structure of the cadherin genes has been studied to only a limited extent. Various independent methods for chromosomal mapping have been used to ascribe the E-cadherin gene to the conserved linkage group on mouse chromosome 8 and the human 16q chromosome (Eistetter et al 1988; Mansouri et al 1988; Scherer et al 1989). Recently, the human N-cadherin gene was shown to be located on a different chromosome (number 18), which rules out the possibility of alternative splicing leading to cadherin diversity and suggests that the N and E-cadherin genes arose by gene duplication (Walsh et al 1990).

The chicken form of E-cadherin (L-CAM) is encoded by a single gene, which is less then 10 kb long. It contains 16 exons and 15 introns, all containing consensus splice sequences, with no consensus junction sequences within the introns themselves. Single axons do not correspond to known protein domains and there is no evidence for alternative splicing of exons in this gene (Sorkin et al 1988).

Attempts to identify cadherins in invertebrates are thus far inconclusive. A molecule that cross-reacts with E-cadherin was recently detected in sea-urchin embryos, but remains to be characterized at the molecular or functional levels (Ghersi & Vittorelli 1990). Attempts to identify cadherins in *Drosophila* focused on the tumor gene *l(2)gl,* which was reported to bear sequence homology to members of the cadherin superfamily (Klambt et al 1989). More recently, Mahoney et al (1991) used the conserved N-terminal and DXNDNXP sequences for cloning a putative cadherin from *Drosophila.* The isolated cDNA encodes 34 cadherin-like repeats and is apparently related to the *fat* mutation. Conclusive evidence confirming the respective protein as an adhesion molecule is still absent.

CYTOPLASMIC, CADHERIN-BINDING PROTEINS: The Catenins

One of the molecular implications of AJ structure and distribution is that cadherins provide a transmembrane linkage to the cytoskeleton. The evidence

that cadherins avidly interact with the cytoskeletal network is based not only on colocalization experiments, but also on the fact that non-ionic detergents, which effectively extract most membrane proteins, do not remove junctional cadherins. Furthermore, transfection experiments with mutated cadherin cDNA indicates that the cytoplasmic domain is essential for the interaction with the cytoskeleton (Nagafuchi & Takeichi 1988; Ozawa et al 1989, 1990). Attempts to identify the cytoplasmic molecules through which this anchorage occurs resulted in the identification of a specific group of proteins--the catenins.

Immunoprecipitation experiments carried out several years ago (Peyrieras et al 1985) indicated that there are several polypeptides that co-immunoprecipitate with uvomorulin antibodies, although they do not directly react with the antibodies on immunoblots. A systematic effort to characterize these molecules indicated that there are at least three independent catenin polypeptides in many cell types (Ozawa et al 1989) that are complexed with E-cadherin. These polypeptides have an apparent molecular mass of 102, 88, and 80 kd (α, β, and γ catenins, respectively) and are apparently also present in cells that contain little or no cadherins. As indicated above, the catenin-recognition site is located within the 72 C-terminal amino acids of cadherins, most of which is encoded by a single exon (Ozawa et al 1990). Using intact cadherin or chimeric constructs in which the cytoplasmic domain of E-cadherin was fused to the extracellular moiety of H-2 kd, these authors showed that the cadherin-catenin complex binds actin and that β catenin is most avidly attached to the cadherin itself (see also McCrea & Gumbiner 1991), while the α-chain mainly affects the binding to actin. Attempts to extend these studies to other cell types suggest that there are both ubiquitous and cell-type-specific catenins (Wheelock 1990; Wheelock & Knudsen 1991).

It is interesting to note that the levels of cadherin may affect catenin expression. It was shown (Nagafuchi et al 1991) that L-cells contain minute amounts of the 102 kd catenin (probably α-catenin) while significant levels of the respective mRNA are present. Transfection of these cells with E-, N- or P-cadherin cDNA resulted in a dramatic increase in the catenin's content, without affecting its mRNA level. This suggests that cadherins may be involved in the stimulation of catenin production at a post-transcriptional level.

So far, little is known of the exact structure of the various catenins except for the α-catenin, which has a deduced structure of five domains. The amino acid sequence of the first, third, and fifth domains share considerable homology with the corresponding domains of vinculin (Nagafuchi et al 1991; Herrenknecht et al 1991).

While the discovery and characterization of catenins provided a major insight into the molecular interactions of cadherins, it is clear that the actual junctional complexes contain a multitude of additional proteins. The isolation of intact junctional complexes in a form amenable to molecular character-

ization is, however, quite difficult. In a study by McCrea & Gumbiner (1991) for example, no other member of AJ was found in association with the cadherin immunoprecipitates, thus indicating that these additional interactions are either labile or transient. On the other hand, Nelson and co-workers (Nelson et al 1990) succeeded in isolating intact cadherin-containing multi-molecular complexes, using a method previously developed to identify Na^+-K^+ ATPase-associated proteins. They showed that cadherin also forms complexes with ankyrin and fodrin, which are known to be peripheral components of the microfilament system. Recent studies suggest that β-catenin apparently is similar to the desmosome- and AJ-associated protein plakoglobin. McCrea & Gumbiner (1991) have sequenced several tryptic peptides of *Xenopus* β-catenin (92 kd) and identified the protein as a homologue of the human plakoglobin and the *Drosophila* armadillo gene product.

CADHERINS AND MALIGNANT TRANSFORMATION

Malignant transformation is often triggered by the expression of a single or several oncogenes, yet the manifestations of the process are highly pleiotropic, affecting both cell structure and behavior. The major manifestation of the transformed phenotype is deregulated cell growth, i.e. the capacity of cells to grow in an anchorage-independent manner (for example in a semisolid medium), and a poor response to so-called contact inhibition (Vasiliev & Gelfand 1981). In addition to the nuclear events, there are also cytoplasmic processes typical of malignant transformation, which include major changes in cell-adhesion and cytoskeletal organization and hence gross alteration in cell shape.

One of the intriguing issues concerning the mechanism of malignant transformation is the causal interrelationship between these two manifestations of malignancy: do changes in growth lead to morphological alteration, are they consequences of this change, or do the two processes develop independently? While in different tumors distinct mechanisms may predominate, there is compelling evidence suggesting that cell adhesions play a central role in regulating cell growth and that adhesive mechanisms are major targets affected by transformation.

The notion that surface or junctional interactions are actually involved in the transduction of growth-regulating signals in normal cells is supported by experiments in which membrane fragments were tested for their capacity to elicit growth inhibition (i.e. Whittenberger & Glaser 1977; Wieser et al 1985, 1988; Wieser & Oesch 1986, 1988). It had further been proposed that the inhibitory effect depends on some surface glycoproteins, yet the exact nature of such molecules is still unknown (Wieser et al 1990). The evidence that cadherins might be involved in the transduction of growth regulatory signals is rather indirect, but is compelling enough to deserve a brief discussion here.

Several series of studies indicated that malignant (especially anaplastic) transformation is often accompanied by a reduced expression of specific cadherins. An immunohistochemical survey of hepatocellular carcinomas showed that while well differentiated tumors contain E-cadherin in intercellular junctions, grade IV tumors, classified as undifferentiated carcinomas, had diminished intercellular adhesion and E-cadherin expression (Shimoyama & Hirohashi 1991a). In gastric adenocarcinomas, variable results were obtained; some tumors contained diminished levels of E-cadherin while others contained this molecule in a poorly organized patterns (Shimoyama & Hirohashi 1991b). The involvement of cadherin depletion in the poor adhesiveness that is characteristic of tumor cells was further demonstrated in a slowly compacting embryonal carcinoma (Littlefield & Whitehouse 1990) and highly metastatic sublines of ovarian carcinoma (Hashimoto et al 1989).

Systematic examination of the interrelationship between cadherin expression in cells and their transformed phenotype was carried out using oncogene-expressing MDCK cells as a model. It was shown that transformation of these cells with the Harvey-*ras* oncogene resulted in the loss of epithelial morphology in culture and the acquisition of malignant properties (Behrens et al 1989; Mareel et al 1991). Examination of these cells not only revealed reduction in E-cadherin expression, but also showed that restoration of this cadherin (by transfection) was accompanied by reformation of epithelial monolayers in culture and loss of malignant growth pattern. These findings are in line with the fact that normal MDCK cells develop invasive properties following treatment with inhibitory antibodies to E-cadherin (Behrens et al 1989). It is important to stress that loss of cadherin expression was not correlated with transformation per se, but rather with the acquisition of a poorly differentiated phenotype, which is common in invasive and metastatic tumors (Frixen et al 1991).

The results presented here suggest that cadherin-mediated interactions have a significant role in maintaining normal growth behavior. The detailed mechanism responsible for this effect is still unknown. One possibility is that cadherin-mediated interactions activate growth inhibitory systems either directly or indirectly through other constituents of the intercellular adherens junctions. Alternatively, the formation of cell-cell junctions may down-regulate substrate adhesion and suppress responsiveness to growth activating factors.

ADHERENS JUNCTIONS AS SIGNAL TRANSDUCTION UNITS

In the previous sections we have considered both the direct cellular consequences of cadherin-mediated interactions, namely the formation of multicellular structures, and some of the long term effects on cell growth. Here, we

briefly consider possible mechanisms that might be involved in the transduction of signals involved in cell growth control and differentiation.

Information on such mechanisms is scarce and therefore we discuss mostly indirect observations that point to topological and functional relationships between the enzymes involved in classical signal transduction pathways and AJ. We refer here to such associations as either cell-matrix or cell-cell AJ since the distinction between the two in the literature is not always unequivocal.

Involvement of protein kinase C (PKC) in adherens junctions is supported by several lines of evidence. These include the apparent association of type 3 PKC with focal contacts (Jaken et al 1989) and the effect of PKC on the organization of AJ. For example, activation of PKC by low levels of phorbol esters leads to premature compaction of mouse embryos and the segregation of E-cadherin into the cell-cell contacts (Winkel et al 1990). This effect, however, does not seem to be universal since in epithelial cells, high PKC activity appears to be correlated with decreased cell-cell adhesion. For example, abrogation of phosphorylation using H-7 and other kinase inhibitors prevents junction dissociation in low-Ca^{2+} medium (Citi 1992). This is largely consistent with the detrimental effect of PKC activation on intercellular interaction in epithelial cells (Schliwa et al 1984). Interestingly phospholipase C-γ, which is involved in the primary activation of PKC, was also localized along actin filaments, enriched at their membrane-bound termini (McBride et al 1991).

Another series of experiments has demonstrated the presence of protein tyrosine phosphorylation in adherens junctions. Immunolocalization of tyrosine phosphorylated molecules showed intense labeling in focal contacts and intercellular AJ (Comoglio et al 1984; Maher et al 1985; Takata & Singer 1988; Volberg et al 1991). Immunolocalization experiments carried out both with transformed and normal cells revealed the presence of several cytoplasmic protein tyrosine kinases associated with these adhesion sites, including the *src* and *yes* gene products (Gentry & Rohrschneider 1984; Nigg et al 1982; Rohrschneider 1980; Rohrschneider & Najita 1984; Tsukita et al 1991).

Attempts to identify specific junctional substrates for these tyrosine kinases indicated that vinculin (Sefton & Hunter 1981), talin (Pasquale et al 1986), paxillin (Glenney & Zokas 1989), and integrins (Hirst et al 1986) may all become phosphorylated on tyrosyl residues, although the functional significance of this modification has not been clearly demonstrated. Nevertheless, the notion that tyrosine phosphorylation might have an effect on junction integrity is supported by several additional observations. These include the deterioration of junctional structures upon transformation with tyrosine kinase oncogenes (Wang & Goldberg 1976) and the changes in junction structure

that occur following modulation of phosphotyrosine levels (Volberg et al 1992). In addition, stimulation of cells with platelet-derived growth factor resulted in the loss of vinculin from adhesion plaques and deterioration of the actin network (Herman & Pledger 1985), and the addition of another tyrosine kinase stimulator, fibroblast growth factor (FGF), to epithelial cells resulted in loss of intercellular adhesion and the acquisition of a more fibroblastoid shape (Boyer & Thiery 1989). In a recent study we have shown that specific inhibition of phosphotyrosine phosphatases results in deterioration of intercellular junctions, while inhibition of tyrosine kinases in transformed cells restores cell junction formation (Volberg et al 1991, 1992). Studies on endothelial cells also indicated that the Ca^{2+}-dependent intercellular adhesion is sensitive to growth factors such as bFGF, aFGF, or ECGF plus heparin (Bavisotto et al 1990).

Finally, several lines of evidence suggest that cadherin-mediated interactions can actually induce cell differentiation. This was especially apparent in neuronal differentiation, characterized by the extension of neurites and acquisition of a highly polarized morphology. It was shown that purified N-cadherin can effectively stimulate neurite outgrowth from cultured chick ciliary ganglion (Bixby & Zhang 1990) and that this or similar processes could be blocked by antibodies to N-cadherin and other adhesion receptors (Drazba & Lemmon 1990; Neugebauer et al 1988; Tomaselli et al 1988; Tomaselli & Reichardt 1988). It had further been claimed that neurite outgrowth stimulated by such adhesion molecules may be modulated by protein kinase C (Bixby & Zhang 1990).

An insight into the possible second messenger pathways that are involved in the cadherin-dependent induction of neural differentiation was recently obtained by Doherty et al (1991), who seeded pheochromocytoma PC12 cells on a monolayer of 3T3 cells, which were transfected with either N-cadherin or N-CAM cDNA, in the absence of NGF. They showed that the transfected monolayer induced a morphological transition in the PC12 cells from the adrenal to the neuronal phenotype. The morphogenetic effect was often more prominent than that obtained with the classical inducer, NGF. It could not be blocked by anti-NGF antibodies, and it did not require new transcription. However, the apparent differentiation could be fully inhibited by pertussis toxin and various Ca^{2+}-channel blockers. These results suggest that calcium ions and pertussis toxin-sensitive G-protein(s) play an indispensable role in the transduction of cadherin-mediated morphogenetic signals.

These and other data provide evidence that the morphogenetic responses to adhesion, mediated through cadherins or other adhesion molecules, involve not only local events, but also long range and long term processes, and use a variety of signal transduction pathways that eventually control growth and differentiation.

CONCLUSION

In this article we have discussed several aspects of cadherin structure and function that bear on the basic mechanisms of contact-dependent regulation of cell behavior. The recent progress in elucidating the chemical properties of these molecules is now paving the way toward understanding adhesion-triggered phenomena at the molecular level. This also sheds light on a series of molecular events that are activated by cell adhesion, or affect adhesive interactions. In this connection, contacts mediated through such surface receptors appear to act as a major signal transduction system in cells. It is anticipated that further elucidation of the molecular events that occur in adhesion sites will provide the molecular answers to questions that have intrigued cell and developmental biologists for decades.

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